APPENDIX A

AU BUREAU CANADIEN DES BREVETS

Brevet canadien No. : 2,406,592

Émis le : 30 septembre 2003

Demandeur : DUCHESNAY INC.

Titre : METHOD OF PREPARING PHARMACEUTICAL DOSAGE FORMS CONTAINING MULTIPLE ACTIVE INGREDIENTS

Notre dossier : 11621.86

AU COMMISSAIRE DES BREVETS
OTTAWA, CANADA

Le 28 septembre 2006

PAIEMENT DE LA TAXE PÉRIODIQUE

Monsieur,

Veuillez trouver ci-joint le versement de $ 100.00 (grande entité) en règlement de la taxe de maintien due le 4 octobre 2006 pour la 4e année du brevet mentionné en rubrique.
Veuillez débiter le montant ci-haut à notre compte N° 600000102.

Si le paiement soumis avec la présente lettre ne suffit pas à couvrir toutes les taxes pour lesquelles un paiement est requis de façon explicite ou implicite, le commissaire est autorisé à prélever la somme manquante sur le compte no. 600000102 déjà au dossier.

Veuillez agréer, Monsieur le Commissaire, nos salutations les plus distinguées.

Par / By: Goudreau Gage Dubuc

GOUDREAU GAGE DUBUC
Agents de Brevets / Patent Agents

JHD/jg
Tél. : (514) 397-4306

IN THE CANADIAN PATENT OFFICE

Canadian patent No : 2,406,592

Issued on : September 30, 2003

Applicant: DUCHESNAY INC.

Title : METHOD OF PREPARING PHARMACEUTICAL DOSAGE FORMS CONTAINING MULTIPLE ACTIVE INGREDIENTS

Our File : 11621.86

2028886

THE COMMISSIONER OF PATENTS
OTTAWA, CANADA

September 28, 2006

PAYMENT OF MAINTENANCE FEE

Sir:

Please find enclosed the payment of 100.00$ (Large Entity) for the maintenance fee due on October 4, 2006 for the 4th year of the above-noted patent.

Please debit the amount above to our Deposit Account N° 600000102.

Should the fees submitted with this letter be insufficient to cover all of the fees for which payment is explicitly or implicitly requested by this letter, the Commissioner is authorized to charge the amount of the insufficiency to our Deposit account no. 600000102 already on file.

Respectfully submitted,

Industry Canada / Industrie Canada
2006/09/28
275 - 06
CIPO OPIC
A000656627

N76675

AU BUREAU CANADIEN DES BREVETS

IN THE CANADIAN PATENT OFFICE

Brevet canadien No. : 2,406,592

Émis le : 30 septembre 2003

Canadian patent No : 2,406,592

Issued on : September 30, 2003

Demandeur : DUCHESNAY INC.

Titre : METHOD OF PREPARING PHARMACEUTICAL DOSAGE FORMS CONTAINING MULTIPLE ACTIVE INGREDIENTS

Applicant: DUCHESNAY INC.

Title : METHOD OF PREPARING PHARMACEUTICAL DOSAGE FORMS CONTAINING MULTIPLE ACTIVE INGREDIENTS

Notre dossier : 11621.86

Our File : 11621.86

AU COMMISSAIRE DES BREVETS
OTTAWA, CANADA

Le 30 septembre 2005

THE COMMISSIONER OF PATENTS
OTTAWA, CANADA

September 30, 2005

PAIEMENT DE LA TAXE PÉRIODIQUE

Monsieur,

Veuillez trouver ci-joint le versement de $ 100.00 (grande entité) en règlement de la taxe de maintien due le 4 octobre 2005 pour la 3e année du brevet mentionné en rubrique.

Veuillez débiter le montant ci-haut à notre compte N° 600000102.

Veuillez agréer, Monsieur le Commissaire, nos salutations les plus distinguées.

PAYMENT OF MAINTENANCE FEE

Sir:

Please find enclosed the payment of 100.00$ (Large Entity) for the maintenance fee due on October 4, 2005 for the 3th year of the above-noted patent.

Please debit the amount above to our Deposit Account N°600000102.

Respectfully submitted,

Goudreau Gage Dubuc

Par / By: _____

GOUDREAU GAGE DUBUC
Agents de Brevets / Patent Agents

JHD/jg
Tél. : (514) 397-4306

Industry Canada Industrie Canada
2005/09/30
277 - 05
CIPO OPIC
B000527118

AU BUREAU CANADIEN DES BREVETS

IN THE CANADIAN PATENT OFFICE

1225993
MDT

Brevet canadien No. : 2,406,592

Canadian patent No : 2,406,592

Émis le : 30 septembre 2003

Issued on : September 30, 2003

Demandeur : DUCHESNAY INC.

Applicant : DUCHESNAY INC.

Titre : METHOD OF PREPARING PHARMACEUTICAL DOSAGE FORMS CONTAINING MULTIPLE ACTIVE INGREDIENTS

Title : METHOD OF PREPARING PHARMACEUTICAL DOSAGE FORMS CONTAINING MULTIPLE ACTIVE INGREDIENTS

Notre dossier : 11621.86

Our File : 11621.86

AU COMMISSAIRE DES BREVETS
OTTAWA, CANADA

Le 1er octobre 2004

THE COMMISSIONER OF PATENTS
OTTAWA, CANADA

October 1, 2004

PAIEMENT DE LA TAXE PÉRIODIQUE

Monsieur,

Veuillez trouver ci-joint le versement de $ 100.00 (grande entité) en règlement de la taxe de maintien due le 4 octobre 2004 pour la 2e année du brevet mentionné en rubrique.

Veuillez débiter le montant ci-haut à notre compte N° 600000102.

Veuillez agréer, Monsieur le Commissaire, nos salutations les plus distinguées.

PAYMENT OF MAINTENANCE FEE

Sir:

Please find enclosed the payment of 100.00$ (Large Entity) for the maintenance fee due on October 4, 2004 for the 2th year of the above-noted patent.

Please debit the amount above to our Deposit Account N° 600000102.

Respectfully submitted,

Goudreau Gage Dubuc

100 K 115

Par / By: _____

Industry Canada / Industrie Canada
2004/10/01
279 - 04
A000279073
CIPO OPIC

GOUDREAU GAGE DUBUC
Agents de Brevets / Patent Agents

JHD/jg
Tél. : (514) 397-4306

Office de la propriété intellectuelle du Canada
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Canadian Intellectual Property Office
An Agency of Industry Canada
www.cipo.gc.ca

GOUDREAU GAGE DUBUC
Tour de la Bourse
Bureau 3400
C.P. 242, 800 Place-Victoria
MONTREAL Quebec
H4Z 1E9

Date : 2004/06/07

Date de dépôt/Filing Date : 2002/10/04
Votre référence/ Your Reference : 11621.86

Titre de l'invention/ Title of Invention : METHOD OF PREPARING PHARMACEUTICAL DOSAGE FORMS CONTAINING MULTIPLE ACTIVE INGREDIENTS

Montant dû/Amount Due : $100.00

Date limite de paiement/ Payment Due Date : 2004/10/04

N° de demande/Application No. : 2,406,592

OBJET: TAXE DE MAINTIEN

La présente a pour but de vous rappeler que pour maintenir votre demande en vigueur, vous devez payer la taxe annuelle au plus tard à la date d'anniversaire du dépôt, à compter du 2e anniversaire.

Vous pouvez payer annuellement ou à l'avance les taxes de maintien pour un nombre d'années donné.

L'omission de payer cette taxe dans les délais fixés résultera en l'abandon de la demande de brevet.

Veuillez prendre note que vous ne recevrez pas d'autre rappel concernant la demande de brevet susmentionnée.

Pour de plus amples renseignements, veuillez communiquer avec le Bureau canadien des brevets au (819) 953-8095.

SUBJECT: MAINTENANCE FEE

You are reminded that, in order to maintain the patent application in force, an annual fee must be paid on or before the anniversary of the filing date, starting with the second anniversary.

The maintenance fees can be paid yearly or for any number of years in advance.

Failure to pay within the prescribed time limit will lead to the abandonment of the patent application.

Please note that this is the only reminder notice that will be issued for this particular application.

Should you require more information, please do not hesitate to contact the Canadian Patent Office at (819) 953-8095.

Commissaire aux brevets/Commissioner of Patents

Canada

OPIC CIPO

661510

012

Goudreau Gage Dubuc
INTELLECTUAL PROPERTY

Direct Dial: *(514) 397-7613*
Internet: *email@ggd.com*
Your Ref.:
Our Ref.: *11621.86*

General Partnership
Patent and Trademark Agents

www.ggd.com

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Quebec City
140 Grande Allée Est
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Quebec, Canada G1R 5M8
Telephone (418) 640-2000

July 4, 2003

The Commissioner of Patents
OTTAWA-HULL CANADA

Subject: Canadian Patent Application S.N. 2,406,592
Classification: 07A61J-00003/06
Allowed Date: June 23, 2003
Applicant: DUCHESNAY INC.
Title: METHOD OF PREPARING PHARMACEUTICAL DOSAGE FORMS CONTAINING MULTIPLE ACTIVE INGREDIENTS

Sir:

Please debit the amount of $300.00 from our Deposit Account no. 600000102 in payment of the final fee of the above-noted application.

Respectfully submitted,

(GOUDREAU) GAGE DUBUC
Goudreau Gage Dubuc

AML/fl

Office de la propriété intellectuelle du Canada
Un organisme d'industrie Canada
www.opic.gc.ca

Canadian Intellectual Property Office
An Agency of Industry Canada
www.cipo.gc.ca

GOUDREAU GAGE DUBUC
Tour de la Bourse
Bureau 3400
C.P. 242, 800 Place-Victoria
MONTREAL Quebec
H4Z 1E9

Date : 2003/06/23
Classification :

AVIS D'ACCEPTATION/NOTICE OF ALLOWANCE

N° de demande/Application No. : 2,406,592 **Date de dépôt/Filing date** : 2002/10/04

Votre référence/ Your Reference : 11621.86

Titre de l'invention/ Title of Invention : METHOD OF PREPARING PHARMACEUTICAL DOSAGE FORMS CONTAINING MULTIPLE ACTIVE INGREDIENTS

Propriétaire(s)/Owner(s) : DUCHESNAY INC.

Revendications/Claims : 010

Examiné tel que modifié/ Examined as amended : 2003/05/09

La demande de brevet susmentionnée a été jugée acceptable.

Il faut payer la taxe finale de CENT CINQUANTE DOLLARS (150 $) ou de TROIS CENTS DOLLARS (300 $) selon que le demandeur est une petite entité ou une grande entité, et ce dans les six mois suivant la date du présent avis. Autrement la demande sera réputée abandonnée en vertu de l'alinéa 73(1)(f) de la Loi sur les brevets.

Une taxe additionnelle de quatre dollars par page excédant 100 pages du mémoire descriptif et dessins devra aussi être payée.

Le brevet sera délivré au nom du dernier propriétaire inscrit à nos dossiers qui a fourni une documentation acceptable, au plus tard à la date du paiement de la taxe finale, conformément à l'article 41 des Règles sur les brevets.

La réponse au présent avis doit comprendre l'identification complète de la demande et la date de l'avis.

La publication des brevets canadiens délivrés dans la Gazette du Bureau des brevets peut comprendre aussi une note concernant la mise en vente d'un brevet ou de sa licence. Si vous désirez profiter de ce service gratuit, veuillez l'indiquer au moment de payer la taxe finale.

The above application for patent has been found allowable.

The final fee of ONE HUNDRED AND FIFTY DOLLARS ($150.00) or THREE HUNDRED DOLLARS ($300.00) depending upon whether the applicant is a small entity or a large entity must be paid within six months following the date of this notice. Otherwise the application will be deemed to be abandoned pursuant to paragraph 73(1)(f) of the Patent Act.

An additional fee of four dollars per page over 100 pages of specification and drawings must also be paid.

The patent shall issue to the last registered owner who has submitted acceptable documentation on or before the date that the final fee is paid (as pursuant to Section 41 of the Patent Rules).

A reply to this notice must include full identification of the application including the date of the notice.

The publication of issued Canadian patents in the Patent Office Record can also include an indication that the patent is available for licence or sale. If you wish to take advantage of this free service, please indicate this when paying the final fee.

Commissaire aux brevets/Commissioner of Patents

008

IN THE CANADIAN PATENT OFFICE

Can. Pat Appln S. N.:	2,406,592	
Filed:	October 4, 2002	
Applicant:	DUCHESNAY INC.	
Title:	METHOD OF PREPARING PHARMACEUTICAL DOSAGE FORMS CONTAINING MULTIPLE ACTIVE INGREDIENTS	
Classification:	07A61J-00003/06	
Our file:	11621.86 AML/hp	

Industry Canada / Industrie Canada
2003/05/09
133 - 03
CIPO OPIC
A000023587

May 9, 2003

THE COMMISSIONER OF PATENTS
OTTAWA CANADA

SIR:

SUPPLEMENTARY AMENDMENT

Following our letter dated April 15, 2003, please amend the above-noted application as follows:

IN THE CLAIMS:

Kindly substitute page 14 of the set of claims for the corresponding page 14 of the set of claims presently on file.

REMARKS:

Claims 1-10 are still in the case.

In claim 7, "The method of any one of claims 1 to 6..." has been changed to -- The method of claim 6 --.

In claim 8, "The method of any one of claims 1 to 6..." has been changed to -- The method of claim 7 --.

Consequently, it is respectfully submitted that all claims are now in condition for allowance and such action is respectfully urged.

Respectfully submitted,
DUCHESNAY INC.

By: _____
GOUDREAU GAGE DUBUC

Alain M. Leclerc, Patent Agent
GOUDREAU GAGE DUBUC
3400 Stock Exchange Tower
P.O. Box 242, Victoria Square
Montréal, Québec, Canada H4Z 1E9
Telephone: (514) 397-7675
E-mail: aleclerc@ggd.com

(d) mixing said granules with at least one other active ingredient and at least one other excipient so as to obtain a granular mixture;

(e) forming said granular mixture into unitary dosage forms.

6. The method of any one of claims 1 to 5 wherein the step of forming said granular mixture into unitary dosage forms comprises compressing said granular mixture into a tablet shape.

7. The method of claim 6 wherein the tablet shape is provided with a coating.

8. The method of claim 7 wherein said coating is an enteric coating.

9. The method of any one of claims 1 to 5 wherein the step of forming said granular mixture into unitary dosage forms comprises loading said granular mixture into an open capsule and thereafter closing said capsule.

10. The method of any one of claims 1 to 9 wherein the active ingredients comprise equal parts of Pyridoxine HCl and Doxylamine Succinate.

IN THE CANADIAN PATENT OFFICE

Can. Pat Appln S. N.:	2,406,592
Filed:	October 4, 2002
Applicant:	DUCHESNAY INC.
Title:	METHOD OF PREPARING PHARMACEUTICAL DOSAGE FORMS CONTAINING MULTIPLE ACTIVE INGREDIENTS
Classification:	07A61J-00003/06
Our file:	11621.86 AML/hp

April 15, 2003

THE COMMISSIONER OF PATENTS
OTTAWA CANADA

SIR:

In response to the Office Action dated March 3, 2003, please amend the above-noted application as follows:

IN THE CLAIMS:

Kindly substitute the enclosed set of claims for the corresponding set of claims presently on file.

REMARKS:

Claims 1-10 are now in the case.

The Examiner is rejected claims 1 to 9 and indicated that claims 10 to 12 are allowable. In order to place this case in condition for allowance, applicant has introduced the subject matter of claim 10 to each of independent claims 1 to 5. Thus, claims 6 to 9 are dependent on allowable claims. Claim 10 is cancelled. Claim 11 is renumbered as claim 10. Claim 12 is cancelled.

Consequently, it is respectfully submitted that all claims are now in condition for allowance and such action is respectfully urged.

Finally, in response to section 29 requirements, applicant advises that at this time there exists no corresponding US, EPO or any other regional office applications.

Respectfully submitted,
DUCHESNAY INC.

By: GOUDREAU GAGE DUBUC

GOUDREAU GAGE DUBUC

Alain M. Leclerc, Patent Agent
GOUDREAU GAGE DUBUC
3400 Stock Exchange Tower
P.O. Box 242, Victoria Square
Montréal, Québec, Canada H4Z 1E9
Telephone: (514) 397-7675
E-mail: aleclerc@ggd.com

WHAT IS CLAIMED IS:

1. A method for the preparation of pharmaceutical dosage forms comprising Pyridoxine HCl and Doxylamine Succinate as active ingredients, said method comprising the steps of:
   (a) mixing said active ingredients and at least one chosen excipient so as to obtain a powdered mixture;
   (b) compacting said powdered mixture in a roller compactor apparatus to obtain a compacted product;
   (c) breaking and sieving said compacted product to a chosen mesh size to obtain similar sized granules;
   (d) forming said granules into unitary dosage forms.

2. A method for the preparation of pharmaceutical dosage forms comprising Pyridoxine HCl and Doxylamine Succinate as active ingredients, said method comprising the steps of:
   (a) mixing said active ingredients and at least one chosen excipient so as to obtain a powdered mixture;
   (b) compacting said powdered mixture in a roller compactor apparatus to obtain a compacted product;
   (c) breaking and sieving said compacted product to a chosen mesh size to obtain similar sized granules;
   (d) mixing said granules with at least one chosen excipient so as to obtain a granular mixture;
   (e) forming said granular mixture into unitary dosage forms.

3. A method for the preparation of pharmaceutical dosage forms comprising Pyridoxine HCl and Doxylamine Succinate as active ingredients, said method comprising the steps of:
   (a) mixing said active ingredients so as to obtain a powdered mixture;

(b) compacting said powdered mixture in a roller compactor apparatus to obtain a compacted product;

(c) breaking and sieving said compacted product to a chosen mesh size to obtain similar sized granules;

(d) mixing said granules with at least one chosen excipient so as to obtain a granular mixture;

(e) forming said granular mixture into unitary dosage forms.

4. A method for the preparation of pharmaceutical dosage forms comprising Pyridoxine HCl and Doxylamine Succinate as active ingredients, said method comprising the steps of:

(a) mixing at least one of said active ingredients and at least one excipient so as to obtain a powdered mixture;

(b) compacting said powdered mixture in a roller compactor apparatus to obtain a compacted product;

(c) breaking and sieving said compacted product to a chosen mesh size to obtain similar sized granules;

(d) mixing said granules with at least one other active ingredient so as to obtain a granular mixture;

(e) forming said granular mixture into unitary dosage forms.

5. A method for the preparation of pharmaceutical dosage forms comprising Pyridoxine HCl and Doxylamine Succinate as active ingredients, said method comprising the steps of:

(a) mixing at least one of said active ingredients and at least one excipient so as to obtain a powdered mixture;

(b) compacting said powdered mixture in a roller compactor apparatus to obtain a compacted product;

(c) breaking and sieving said compacted product to a chosen mesh size to obtain similar sized granules;

(d) mixing said granules with at least one other active ingredient and at least one other excipient so as to obtain a granular mixture;

(e) forming said granular mixture into unitary dosage forms.

6. The method of any one of claims 1 to 5 wherein the step of forming said granular mixture into unitary dosage forms comprises compressing said granular mixture into a tablet shape.

7. The method of any one of claims 1 to 6 wherein the tablet shape is provided with a coating.

8. The method of any one of claims 1 to 6 wherein said coating is an enteric coating.

9. The method of any one of claims 1 to 5 wherein the step of forming said granular mixture into unitary dosage forms comprises loading said granular mixture into an open capsule and thereafter closing said capsule.

10. The method of any one of claims 1 to 9 wherein the active ingredients comprise equal parts of Pyridoxine HCl and Doxylamine Succinate.

March 3, 2003

GOUDREAU GAGE DUBUC
Tour de la Bourse
Bureau 3400
C.P. 242, 800 Place-Victoria
MONTREAL Quebec
H4Z 1E9

Application No.	:	**2,406,592**
Owner	:	DUCHESNAY INC.
Title	:	**METHOD OF PREPARING PHARMACEUTICAL DOSAGE FORMS CONTAINING MULTIPLE ACTIVE INGREDIENTS**
Classification	:	A61J-3/06
Your File No.	:	**11621.86**
Examiner	:	Ishtiaque I. Rashid

IN ACCORDANCE WITH SUBSECTION 30(2) OF THE PATENT RULES, YOU ARE HEREBY NOTIFIED OF A REQUISITION BY THE EXAMINER. IN ORDER TO AVOID ABANDONMENT UNDER PARAGRAPH 73(1)(A) OF THE PATENT ACT, A WRITTEN REPLY MUST BE RECEIVED WITHIN 6 MONTHS AFTER THE ABOVE DATE.

This application has been examined taking into account applicant's correspondence dated December 9, 2002.

The number of claims in this application is 12.

A search of the prior art has revealed the following:

References Applied:

Canadian Patent Application

2224269	Jan. 9, 1997	A61K-31/565	De Haan et al

De Haan et al disclose a method for the preparation of pharmaceutical dosage forms comprising multiple powdered active ingredients, said method comprising the steps of: mixing said active ingredients and at least one chosen excipient so as to obtain a powdered mixture; compacting said powdered mixture in a roller compactor apparatus to obtain a compacted product; breaking and sieving said compacted product to a chosen mesh size to obtain similar sized granules and forming said granules into unitary dosage forms. A step of mixing said granules with an excipient so as to obtain a granular mixture, before forming said granular mixture into unitary dosage forms is also disclosed in another embodiment of the invention.

The examiner has identified the following defects in the application:

Claims 1 to 6 do not comply with Paragraph 28.2(1)(b) of the Patent Act. De Haan et al disclosed the claimed subject matter before the claim dates.

From the above, it is clear that no novelty can be found in the claims.

Claims 7 to 9 do not comply with Section 28.3 of the Patent Act. The subject matter of these claims would have been obvious on the claim date to a person skilled in the art or science to which they pertain having regard to De Haan et al in light of common general knowledge. The major elements are found in De Haan whereas the fact that the resulting tablets are provided with an enteric coating is well known in the art and thus lacks an inventive step. The same can be said about the granular mixture which is placed into the capsules. These elements by themselves are so common in the pharmaceutical manufacturing industry, that they are not considered to be patentable.

Under Section 29 of the Patent Rules, applicant is requisitioned to provide an identification of any prior art cited in respect of the corresponding United States, European Patent Office and any other regional office applications and the patent numbers, if granted. Amendment to avoid references cited abroad may expedite the prosecution. If the particulars are not available to the applicant, the reason why must be stated. Accordingly, if the applicant did not apply for a patent in a foreign country, it must be stated.

The above requisitioned information must be provided regardless of the current status of the foreign applications.

Claims 10 to 12 appear to be acceptable at this point of the examination.

In view of the foregoing defects, the applicant is requisitioned to amend the application in order to comply with the Patent Act and the Patent Rules or to provide arguments as to why the application does comply.

Ishtiaque I. Rashid
Patent Examiner
(819) 953-0787
2406592A.lir

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Un organisme d'Industrie Canada
www.opic.gc.ca

Canadian Intellectual Property Office
An Agency of Industry Canada
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GOUDREAU GAGE DUBUC
Tour de la Bourse
Bureau 3400
C.P. 242, 800 Place-Victoria
MONTREAL Quebec
H4Z 1E9

Date : 2003/02/17

ACCUSE DE RECEPTION DE LA REQUETE D'EXAMEN
ACKNOWLEDGEMENT OF REQUEST FOR EXAMINATION

N° de demande/Application No. : 2,406,592 **Classification :**

Votre référence/Your Reference : 11621.86

Titre de l'invention/ Title of Invention : METHOD OF PREPARING PHARMACEUTICAL DOSAGE FORMS CONTAINING MULTIPLE ACTIVE INGREDIENTS

Propriétaire(s)/Owner(s) : DUCHESNAY INC.

Nous accusons réception de la requête et de la taxe prescrite.

L'examen de la demande suivra son cours.

Il serait à l'avantage du demandeur de fournir les détails de toutes les antériorités citées à l'égard de la demande correspondante aux États-Unis et en Europe lorsqu'elles seront disponibles. De plus, afin de faciliter la procédure d'examen de cette demande, il serait utile de nous envoyer une copie de toutes les citations qui ne sont pas des brevets.

Veuillez ne pas tenir compte du paragraphe précédent si vous avez déjà soumis les antériorités.

The Request for Examination and prescribed fee have been received.

Examination of the application will take place in due course.

It would be to an applicant's advantage to furnish particulars of the prior art cited in respect of the corresponding applications before the United States Patent Office and European Patent Office when such information becomes available. Furthermore, in order to assist in the examination of this application, a copy of all non-patent citations would be appreciated.

If prior art has already been submitted, please disregard the above paragraph.

L. Roussel

February 17, 2003

GOUDREAU GAGE DUBUC
Tour de la Bourse
Bureau 3400
C.P. 242, 800 Place-Victoria
MONTREAL Quebec
H4Z 1E9

Application No.	:	**2,406,592**
Owner	:	DUCHESNAY INC.
Title	:	**METHOD OF PREPARING PHARMACEUTICAL DOSAGE FORMS CONTAINING MULTIPLE ACTIVE INGREDIENTS**
Classification	:	A61J-3/06
Your File No.	:	**11621.86**

Dear Sir/Madam:

Replying to your letter of December 9, 2002, a Special Order will be granted when the application is laid open and the application will be advanced out of its routine order for examination at that time.

Also, your request for examination and your request for an early laid-open date have been made of record. The laid-open date is April 17, 2003.

Yours truly,

Line Roussel
Head, Exam Support, Unit 3
(819) 997-7663

Office de la propriété intellectuelle du Canada
Un organisme d'Industrie Canada
www.opic.gc.ca

Canadian Intellectual Property Office
An Agency of Industry Canada
www.cipo.gc.ca

GOUDREAU GAGE DUBUC
Tour de la Bourse
Bureau 3400
C.P. 242, 800 Place-Victoria
MONTREAL Quebec
H4Z 1E9

Date : 2003/01/22

Votre référence/Your Reference : 11621.86

ENREGISTREMENT/REGISTRATION 05201964

CESSION DROIT EXCLUSIF
ASSIGNMENT FULL INTEREST

DE/FROM VEILLEUX, GISELE; SHULMAN, VICTOR; GERVAIS, ERIC

A/TO DUCHESNAY INC.

Un document a été enregistré au Bureau des brevets, visant le ou les numéros de brevet(s) et/ou de demande(s) de brevet, apparaissant ci-dessous.

A document has been registered in the Patent Office, against the following patent(s) and/or application(s) for patent.

DEMANDE(S)/APPLICATION(S)
2,406,592

SLAUDER
Commis aux cessions de brevets/Patent Assignment Clerk

Canada

OPIC CIPO

1020232

IN THE CANADIAN PATENT OFFICE

007 022
011
00

Can. Pat. Appln. S.N.:	2,406,592	
Filed:	October 4, 2002	C/A # 6102 K122 3702 B#
Applicant:	DUCHESNAY INC.	
Title:	METHOD OF PREPARING PHARMACEUTICAL DOSAGE FORMS CONTAINING MULTIPLE ACTIVE INGREDIENTS	
Our File:	11621.86	

DEPOT POUR REC. GEN. DU CANADA 033-13655 9881-10 09-87913
400.00
020 0001-002 3:02PM 12/12/02

6 Industrie Canada OPIC Industry Canada CIPO 6

December 9, 2002

DEC - 9 2002 3 45

THE COMMISSIONER OF PATENTS
OTTAWA CANADA

Sir:

Pursuant to Section 35 of the Patent Act, applicant hereby request the examination of the above-noted application. A voluntary amendment is also enclosed.

Pursuant to Section 28 (1) of the Patent Rules, applicant also requests the advancement of the examination in view of possible infringement. It is believed that failure to advance this application is likely to prejudice applicant's right.

Finally, according to section 10(2) of the Patent Act, the applicant hereby requests that the above-noted application be published as soon as possible.

Please debit the amount of $500.00 from our Deposit Account no. 600000102 in payment of the prescribed fee of $400.00 for filing the examination request and the prescribed fee of $100.00 for the advancement requests.

Respectfully submitted

DUCHESNAY INC.

By: GOUDREAU GAGE DUBUC

Alain M. Leclerc
Patent Agent
(514) 397-7675

DEPOT POUR REC. GEN. DU CANADA 033-13655 9881-10 09-87913
C/A # 6102 K116 3702 B#
100.00
020 0001-002 3:02PM 12/12/02

IN THE CANADIAN PATENT OFFICE

Can. Pat Appln S. N.:	2,406,592
Filed:	October 4, 2002
Applicant:	Duchesnay Inc.
Title:	METHOD OF PREPARING PHARMACEUTICAL DOSAGE FORMS CONTAINING MULTIPLE ACTIVE INGREDIENTS
Classification:	Unknown
Our file:	AML/11621.86

December 9, 2002

THE COMMISSIONER OF PATENTS
OTTAWA CANADA

SIR:

VOLUNTARY AMENDMENT

Applicant submit the following amendment to the above-noted patent application in order to correct typographical errors.

IN THE DISCLOSURE:

Kindly replace pages 5, 6 and 7 presently on file by the corresponding pages 5, 6 and 7 enclosed.

IN THE CLAIMS:

Kindly substitute the enclosed page containing claims 6 to 12 for the corresponding page presently on file.

REMARKS:

On page 5, paragraph [0013], line 4, the word "compacted" was replaced by the word --compressed--.

On page 6, paragraph [0017]:

- the word "friable" was deleted on line 2;
- on lines 3-4, words "are examples" were replaced by –is an example–; and
- on line 8, the word "harness" was corrected to read –hardness–.

On page 7, second line, the word "vibrating" was deleted.

On claim 8, reference is now to claims 1 to 7.

No new matter has been entered as a result of this amendment.

Favourable consideration of this case is respectfully requested.

Respectfully submitted,

DUCHESNAY INC.

By: GOUDREAU GAGE DUBUC
GOUDREAU GAGE DUBUC

Alain M. Leclerc, Patent Agent
GOUDREAU GAGE DUBUC
Telephone (514) 397-7675
Internet: aleclerc@ggd.com

BRIEF DESCRIPTION OF THE DRAWING

[0009] In the appended drawing:

[0010] Figure 1 is a flowchart of a preferred embodiment of the manufacturing method steps of the present invention.

DESCRIPTION OF THE PREFERRED EMBODIMENT

[0011] When used herein, the term "active ingredient" refers to a therapeutically active substance. "Therapeutically active substance" is to be understood to encompass vitamins or nutritional supplements.

[0012] When used herein, the term "medicament" refers to a pharmaceutical dosage form comprising one or more active ingredients and one or more excipients and optionally one or more coatings.

[0013] The prior art method of manufacturing Diclectin®, a medicament containing a synergistic duo of active ingredients consisted of dry mixing the active ingredients along with excipients; the mixed powder was then compressed into a tablet shape and appropriately coated.

[0014] It has now been found against expectations that the use of a roller compactor alleviates active ingredient losses during manufacturing. As an added benefit, content uniformity in terms of active ingredients is vastly improved because the particle size of active ingredients may now be standardized thereby avoiding poor mixing of active ingredients or losses due to fines which adhere to processing equipment or which do not flow properly. Indeed, roller compaction allows fine powders to be augmented to larger size particles that are less prone to cause ingredient losses during processing.

[0015] In the preferred embodiment wherein at least two active ingredients are roller compacted together, additional benefits are apparent. In such case, the powdered active ingredients are augmented in particle size in a physically combined entity of the active ingredients. This entity now resists particle segregation upon mixing and allows for improved mixing of the two active ingredients.

[0016] Referring to Figure 1, there is shown a schematic flowchart of a preferred embodiment of the process of the present invention. In general terms, in a first step **10**, the active ingredients are mixed, preferably dry mixed, with at least one chosen excipient to obtain a powdered mixture. The next step **20** is to submit the powdered mixture to roller compaction to obtain a compacted product. In step **30** the compacted product is broken and sieve to a chosen mesh size. Step **40** is an optional step wherein the resulting granulate of step **30** is mixed with one or more excipients and or other active ingredients. In step **50**, the resulting product from step **40** is loaded into a final dosage form such as a tablet shape obtained by compression.

[0017] A roller compactor is essentially a piece of equipment capable of compacting a powdered substance into a compacted product. The Chilsonator® sold by Fitzpatrick Company of Elmhurst, Illinois, USA is an example of such equipment. Roller compactors are commonly provided with a hopper into which the powdered substance is loaded. Counter-rotating rollers force the powdered substance between compaction rollers below or to the side of the hopper discharge. The shape of the resulting compacted product, its hardness and density are essentially dictated by the relative distance and speed of the rollers, the speed of the hopper infeed and the compaction properties of the materials being compacted.

[0018] When using a roller compactor to compact an initial blend of powdered ingredients, the resulting compacted product may be broken and

sieved to a chosen mesh size to achieve a specified granule size distribution. To this end, a breaking rotor or wheel and a mesh screen are commonly used. Fines are usually discarded or recycled back into the hopper. The resulting granulate may be further blended to ensure content uniformity of initial ingredients throughout the resulting granulate.

[0019] In essence, the compaction process removes entrapped air from interstices of the initial substance and forms denser granules when broken. Also, fine powders having poor flow characteristics and subject to electrostatic charge causing unwanted adhere to processing or storage equipment, once subjected to roller compaction, are upgraded in size to larger granules which are less prone to cause ingredient losses during processing or storage.

[0020] Furthermore, since the resulting granulate is of essentially uniform size distribution, the problem of size difference of the initial powdered ingredients is addressed. For example, the ingredient Pyridoxine HCl and Doxylamine Succinate are no longer of different mean particle diameter and are of a mean particle diameter large enough to prevent excessive loss of Pyridoxine HCl during processing.

[0021] Example 1 below is a demonstration of active ingredient loss using a prior art manufacturing method. Example 2 that follows example 1 is a demonstration that such active ingredient loss is negated when practicing the method of the present invention.

[0022] **Example 1 (prior art)**

[0023] Active ingredients, namely Pyridoxine HCl and Doxylamine Succinate were blended with exact quantities of excipients. Five samples of 3 grams were placed into small polyethylene bags and shaken. This mimics the prior art method of placing a final blend of active ingredients and excipients into

6. The method of any one of claims 1 to 5 wherein the step of forming said granular mixture into unitary dosage forms comprises compressing said granular mixture into a tablet shape.

7. The method of any one of claims 1 to 6 wherein the tablet shape is provided with a coating.

8. The method of any one of claims 1 to 7 wherein said coating is an enteric coating.

9. The method of any one of claims 1 to 5 wherein the step of forming said granular mixture into unitary dosage forms comprises loading said granular mixture into an open capsule and thereafter closing said capsule.

10. The method of any one of claims 1 to 9 wherein the active ingredients comprise Pyridoxine HCl and Doxylamine Succinate.

11. The method of any one of claims 1 to 9 wherein the active ingredients comprise equal parts of Pyridoxine HCl and Doxylamine Succinate.

12. The method of any one of claims 1 to 9 wherein the active ingredients consist of equal parts of Pyridoxine HCl and Doxylamine Succinate.

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Goudreau Gage Dubuc
INTELLECTUAL PROPERTY

1 Industrie Canada CIPO Industry Canada CIPO 1

DEC 3 - 2002 3 39

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Your Ref.:
Our Ref.: *11621.86*

December 3, 2002

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The Commissioner of Patents
OTTAWA-HULL CANADA

Subject: Can. Pat. Appln. S.N. 2,406,592
Filed: October 4, 2002
Title: METHOD OF PREPARING PHARMACEUTICAL DOSAGE FORMS CONTAINING MULTIPLE ACTIVE INGREDIENTS

Sir:

We enclose an assignment for recording against the above-noted application. Please debit the amount of $100.00 from our Deposit Account no. 600000102.

Respectfully submitted,

Goudreau Gage Dubuc

AML/fi

100.00

ASSIGNMENT OF INVENTION

UNIVERSAL

WHEREAS, we, undersigned, **GISÈLE VEILLEUX**, residing and domiciled at 5420, rue Pasquier, Laval, Québec, Canada, H7K 2X3, **VICTOR SHULMAN**, residing and domiciled at 33, Rosemount Avenue, Thornhill, Ontario, Canada, L3T 6S8 and **ÉRIC GERVAIS**, residing and domiciled at 2526, des Oiseaux, Laval, Québec, Canada H7L 4W9, have invented certain improvements described in a patent application filed in Canada on October 4, 2002 under application number 2,406,592 and entitled:

METHOD OF PREPARING PHARMACEUTICAL DOSAGE FORMS CONTAINING MULTIPLE ACTIVE INGREDIENTS

and:

WHEREAS, **DUCHESNAY INC.**, a body corporate duly incorporated under the laws of the province of Québec, having is head office and principal place of business at 2925, boulevard Industriel, Laval, Québec, Canada, H7L 3W9 (hereinafter referred to as the "Assignee"), is desirous of acquiring the entire right, title and interest in and to said invention or inventions and in and to any and all patents obtained therefore in any country;

NOW, THEREFORE, in consideration of One Dollar ($1.00) and other valuable consideration, the receipt of which is hereby acknowledged, we have and by these presents do hereby sell, assign and transfer unto said Assignee, its successors and assigns, the entire right, title and interest in and to said invention or inventions, as described in the aforesaid patents, in any form or embodiment thereof, also the entire right, title and interest in and to any and all reissues or extensions thereof to be obtained in any country upon said invention or inventions.

We further agree without any payment by said Assignee other than expenses incurred by the undersigned, to communicate to said Assignee, its representatives or agents, any facts relating to said invention or inventions, including evidence for interference purposes or for other proceedings, whenever requested; testify in any interference, litigation or other proceedings, whenever requested; and execute and deliver, on request, all lawful papers required to make any of the foregoing provisions effective, and likewise make these provisions binding upon our heirs, legal representatives, administrators and assigns.

.../2

ASSIGNMENT OF INVENTION
UNIVERSAL
METHOD OF PREPARING PHARMACEUTICAL DOSAGE FORMS CONTAINING MULTIPLE ACTIVE INGREDIENTS

Les soussignés désirent que la présente cession soit en anglais. The undersigned request that the present assignment be in English.

IN WITNESS WHEREOF, we have hereunto set our hands and seal this 28th day of November 2002, with a retroactive effect to October 4, 2002.

Commissioner of Oaths for the judicial district of Montreal, province of Quebec, Canada

Gisèle Veilleux

Commissioner of Oaths for the judicial district of Montreal, province of Quebec, Canada

Victor Shulman

Commissioner of Oaths for the judicial district of Montreal, province of Quebec, Canada

Éric Gervais

November 26, 2002

GOUDREAU GAGE DUBUC
Tour de la Bourse
Bureau 3400
C.P. 242, 800 Place-Victoria
MONTREAL Quebec
H4Z 1E9

Application No.	:	**2,406,592**
Owner	:	DUCHESNAY INC.
Title	:	**METHOD OF PREPARING PHARMACEUTICAL DOSAGE FORMS CONTAINING MULTIPLE ACTIVE INGREDIENTS**
Your File No.	:	**11621.86**

EVIDENCE/COURTESY LETTER

Filing Date: October 4, 2002
Due Date: October 4, 2003

The applicant is advised that in the case where applicants are not the inventors, evidence, by way of affidavit, statutory declaration or copies of documents effecting transfers or changes of name establishing that the applicant is a legal representative of the inventor must be provided. Any document supplied for this purpose must be registered in the Canadian Patent Office. The fee for registration is $100.00 per document.

The providing of evidence is not a completion requirement and no completion fee is required. However, if the documents are not received in the Canadian Patent Office on or before the due date specified above, the Patent Office will send a further letter requisitioning the required documents within a 3 month time limit set under section 25 of the Patent Rules.

Ms. Lyne Éthier
Patent Formalities Clerk
819-953-7554

Office de la propriété intellectuelle du Canada
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An Agency of Industry Canada
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MONTREAL Quebec
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Date : 2002/11/19

FILING CERTIFICATE

Application No.	: **2,406,592**	**Filing Date**	: 2002/10/04
Expected Laid-Open Date	: 2004/04/04	**Your Reference**	: 11621.86

Title of Invention : METHOD OF PREPARING PHARMACEUTICAL DOSAGE FORMS CONTAINING MULTIPLE ACTIVE INGREDIENTS

Applicant(s) : DUCHESNAY INC.

Inventor(s) : VEILLEUX, GISELE; SHULMAN, VICTOR; GERVAIS, ERIC

Special Notice

You are reminded that annual fees to maintain your application are needed for each one-year period between the 2nd and 20th anniversaries and must be paid on or before each anniversary. Failure to pay within the prescribed time limit will lead to abandonment of your application.

Commissioner of Patents

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Goudreau Gage Dubuc

INTELLECTUAL PROPERTY

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OCT 04 2002 2 8 1

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140 Grande Allée Est
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Quebec, Canada G1R 5M8
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October 4, 2002

The Commissioner of Patents
OTTAWA-HULL CANADA

Subject: Inventor: VEILLEUX, Gisèle et al
Applicant: DUCHESNAY INC.
Title: METHOD OF PREPARING PHARMACEUTICAL DOSAGE FORMS CONTAINING MULTIPLE ACTIVE INGREDIENTS

Sir:

We enclose for filing a patent application consisting of the following documents and fees:

- Petition
- Abstract
- Disclosure and claims
- Drawings
- Fees: Filing $300.00

DEPOT FOUR REV. GEN.
DU CANADA 033-13655
0881-10 09-87913
C/A # 6102
K121
8914 BH 012 0001-201 10/OCT/02 10/ 9/02
300.00

Priority is hereby claimed, based on:

S.N.: n/a
Date: n/a
Country: n/a

Please debit the amount of $300.00 from our Deposit Account no. 600000102.

Respectfully submitted,

Goudreau Gage Dubuc

AML/fl

PETITION FOR GRANT OF A PATENT

1 Industrie Canada OPIC Industry Canada CIPO 1

OCT 04 2002 2 8 1

Dossier Pho
Fonds J

1. The applicant DUCHESNAY INC.

whose complete address is 2925, boulevard Industriel, Chomedey, Laval, Quebec, Canada H7L 3W9

requests the grant of a patent for an invention, entitled **"METHOD OF PREPARING PHARMACEUTICAL DOSAGE FORMS CONTAINING MULTIPLE ACTIVE INGREDIENTS"**

which is described and claimed in the accompanying specification.

2. ~~This application is a division of application number filed in Canada on .~~

3. ~~(1) The applicant is the sole inventor.~~

(2) The inventors 1) VEILLEUX, Gisèle; 2) SHULMAN, Victor; and 3) GERVAIS, Éric

whose complete addresses are 1) 5420, rue Pasquier, Laval, Quebec, Canada H7K 2X3; 2) 33 Rosemount Avenue, Thornhill, Ontario, Canada L3T 6S8; and 3) 2526, boulevard des Oiseaux, Laval, Quebec, Canada H7L 3W9

and the applicant own in Canada the whole interest in the invention.

4. The applicant requests priority in respect of the application on the basis of the following previously regularly filed application:

Country of filing	Application number	Filing date
n/a	n/a	n/a

5. The applicant appoints **GOUDREAU GAGE DUBUC** whose complete address in Canada is 3400, The Stock Exchange Tower, P.O. Box 242, Victoria Square, Montreal, Quebec H4Z 1E9, telephone (514) 397-7602, telecopier (514) 397-4382, Canada, as the applicant's representative in Canada, pursuant to section 29 of the *Patent Act*.

6. The applicant appoints **GOUDREAU GAGE DUBUC,** whose complete address is 3400, The Stock Exchange Tower, P.O. Box 242, Victoria Square, Montreal, Quebec H4Z 1E9, telephone (514) 397-7602, telecopier (514) 397-4382, Canada, as the applicant's patent agent.

7. ~~The applicant believes that the applicant is entitled to claim status as a "small entity" as defined under section 2 of the *Patent Rules*.~~

8. The applicant requests that Figure No. 1 of the drawings accompany the abstract when it is open to public inspection under section 10 of the *Patent Act* or published.

Signed at MONTREAL QUEBEC CANADA

this 4th day of October 2002

DUCHESNAY INC.

By: GOUDREAU GAGE DUBUC

ABSTRACT OF THE DISCLOSURE

A method for the preparation of pharmaceutical dosage forms comprising multiple powdered active ingredients, in a preferred embodiment, said method comprising the steps of mixing said active ingredients and at least one chosen excipient so as to obtain a powdered mixture; compacting said powdered mixture in a roller-compactor apparatus to obtain a compacted product; breaking and sieving said compacted product to a chosen mesh size to obtain similar sized granules; preferably dry mixing said granules with at least on chosen excipient so as to obtain a granular mixture; forming said granular mixture into unitary dosage forms.

TITLE OF THE INVENTION

Method of preparing pharmaceutical dosage forms containing multiple active ingredients

FIELD OF THE INVENTION

[0001] The present invention relates to a method of preparing pharmaceutical dosage forms containing multiple active ingredients. More specifically, the present invention is concerned with alleviating active ingredient losses during manufacturing and ensuring content uniformity of dosage forms.

BACKGROUND OF THE INVENTION

[0002] A number of pharmaceutical dosage forms comprise multiple active ingredients. One example is the anti-nauseant medicament prescribed during pregnancy currently sold in Canada under the trademark Diclectin®.

[0003] Diclectin® is a medicament containing a synergistic duo of active ingredients, namely Doxylamine Succinate and Pyridoxine HCl. In the case of Diclectin®, the approved label of the product calls for the duo of active ingredients to be present in exactly equal amounts of 10 mg. These active ingredients are obtained in the form of powders having different granular sizes which makes it very difficult to uniformly mix them in a dry state along with required excipients. Such phenomenon is generally caused by particle segregation during mixing. This poses a content uniformity challenge during manufacturing of final dosage forms.

[0004] An added challenge to content uniformity is the loss of the active ingredient Pyridoxine HCl during manufacturing of Diclectin®. Pyridoxine HCl is generally provided as a crystalline powder having a mean particle diameter of about 60 microns. In contrast, Doxylamine Succinate is

composed of rod shaped particles having a mean particle diameter of about 200 microns. It has been observed that due to their small size and possible electrostatic charge, Pyridoxine HCl particles tend to easily adhere to manufacturing vessels and other processing or storage equipment. Thus, when processing both active ingredients through the same equipment, more Pyridoxine HCl is lost than Doxylamine Succinate. To compensate for this effect, operators have commonly used a 8-10 weight percent overage of Pyridoxine HCl in comparison to Doxylamine Succinate. However, the result of such method is somewhat irregular and quality controls still reject many lots.

[0005] In general terms, whenever preparing multi-ingredient medicaments, it is important that manufacturing methods allow for the final content of each dosage form to follow rather exactly the contents announced on the label. This is indeed a legal and regulatory requirement in most countries of the world.

[0006] Thus, there is a need for a method of manufacturing Diclectin® or other similar powderous multi-ingredient medicaments which alleviate ingredient losses during manufacturing and provides superior content uniformity results when compared to known methods.

OBJECTS OF THE INVENTION

[0007] Objects of the present invention are therefore to provide an improved method of preparing pharmaceutical dosage forms containing multiple active ingredients so as to ensure active ingredient content uniformity and to alleviate active ingredient losses during manufacturing.

SUMMARY OF THE INVENTION

More specifically, in accordance with the present invention, there is provided a method for the preparation of pharmaceutical dosage forms comprising multiple powdered active ingredients, said method comprising the steps of:

(a) mixing said active ingredients and at least one chosen excipient so as to obtain a powdered mixture;
(b) compacting said powdered mixture in a roller compactor apparatus to obtain a compacted product;
(c) breaking and sieving said compacted product to a chosen mesh size to obtain similar sized granules;
(d) forming said granules into unitary dosage forms.

In another aspect, the method may comprise the steps of:

(a) mixing said active ingredients and at least one chosen excipient so as to obtain a powdered mixture;
(b) compacting said powdered mixture in a roller compactor apparatus to obtain a compacted product;
(c) breaking and sieving said compacted product to a chosen mesh size to obtain similar sized granules;
(d) mixing said granules with at least one chosen excipient so as to obtain a granular mixture;
(e) forming said granular mixture into unitary dosage forms.

In yet another aspect, the method may comprise the steps of:

(a) mixing said active ingredients so as to obtain a powdered mixture;
(b) compacting said powdered mixture in a roller compactor apparatus to obtain a compacted product;
(c) breaking and sieving said compacted product to a chosen mesh size to obtain similar sized granules;
(d) mixing said granules with at least one chosen excipient so as to obtain a granular mixture;
(e) forming said granular mixture into unitary dosage forms.

In yet another aspect, the method may comprise the steps of:

(a) mixing at least one of said active ingredients and at least one excipient so as to obtain a powdered mixture;

(b) compacting said powdered mixture in a roller compactor apparatus to obtain a compacted product;

(c) breaking and sieving said compacted product to a chosen mesh size to obtain similar sized granules;

(d) mixing said granules with at least one other active ingredient so as to obtain a granular mixture;

(e) forming said granular mixture into unitary dosage forms.

In yet another aspect, the method may comprise the steps of:

(a) mixing at least one of said active ingredients and at least one excipient so as to obtain a powdered mixture;

(b) compacting said powdered mixture in a roller compactor apparatus to obtain a compacted product;

(c) breaking and sieving said compacted product to a chosen mesh size to obtain similar sized granules;

(d) mixing said granules with at least one other active ingredient and at least one other excipient so as to obtain a granular mixture;

(e) forming said granular mixture into unitary dosage forms.

[0008] Other aspects, objects, advantages and features of the present invention will become more apparent upon reading of the following non-restrictive description of preferred embodiments thereof, given by way of example only with reference to the accompanying drawing.

BRIEF DESCRIPTION OF THE DRAWING

[0009] In the appended drawing:

[0010] Figure 1 is a flowchart of a preferred embodiment of the manufacturing method steps of the present invention.

DESCRIPTION OF THE PREFERRED EMBODIMENT

[0011] When used herein, the term "active ingredient" refers to a therapeutically active substance. "Therapeutically active substance" is to be understood to encompass vitamins or nutritional supplements.

[0012] When used herein, the term "medicament" refers to a pharmaceutical dosage form comprising one or more active ingredients and one or more excipients and optionally one or more coatings.

[0013] The prior art method of manufacturing Diclectin®, a medicament containing a synergistic duo of active ingredients consisted of dry mixing the active ingredients along with excipients; the mixed powder was then compacted into a tablet shape and appropriately coated.

[0014] It has now been found against expectations that the use of a roller compactor alleviates active ingredient losses during manufacturing. As an added benefit, content uniformity in terms of active ingredients is vastly improved because the particle size of active ingredients may now be standardized thereby avoiding poor mixing of active ingredients or losses due to fines which adhere to processing equipment or which do not flow properly. Indeed, roller compaction allows fine powders to be augmented to larger size particles that are less prone to cause ingredient losses during processing.

[0015] In the preferred embodiment wherein at least two active ingredients are roller compacted together, additional benefits are apparent. In such case, the powdered active ingredients are augmented in particle size in a physically combined entity of the active ingredients. This entity now resists particle segregation upon mixing and allows for improved mixing of the two active ingredients.

[0016] Referring to Figure **1**, there is shown a schematic flowchart of a preferred embodiment of the process of the present invention. In general terms, in a first step **10**, the active ingredients are mixed, preferably dry mixed, with at least one chosen excipient to obtain a powdered mixture. The next step **20** is to submit the powdered mixture to roller compaction to obtain a compacted product. In step **30** the compacted product is broken and sieve to a chosen mesh size. Step **40** is an optional step wherein the resulting granulate of step **30** is mixed with one or more excipients and or other active ingredients. In step **50**, the resulting product from step **40** is loaded into a final dosage form such as a tablet shape obtained by compression.

[0017] A roller compactor is essentially a piece of equipment capable of compacting a powdered substance into a friable compacted product. The Chilsonator® sold by Fitzpatrick Company of Elmhurst, Illinois, USA are examples of such equipment. Roller compactors are commonly provided with a hopper into which the powdered substance is loaded. Counter-rotating rollers force the powdered substance between compaction rollers below or to the side of the hopper discharge. The shape of the resulting compacted product, its harness and density are essentially dictated by the relative distance and speed of the rollers, the speed of the hopper infeed and the compaction properties of the materials being compacted.

[0018] When using a roller compactor to compact an initial blend of powdered ingredients, the resulting compacted product may be broken and

sieved to a chosen mesh size to achieve a specified granule size distribution. To this end, a breaking rotor or wheel and a vibrating mesh screen are commonly used. Fines are usually discarded or recycled back into the hopper. The resulting granulate may be further blended to ensure content uniformity of initial ingredients throughout the resulting granulate.

[0019] In essence, the compaction process removes entrapped air from interstices of the initial substance and forms denser granules when broken. Also, fine powders having poor flow characteristics and subject to electrostatic charge causing unwanted adhere to processing or storage equipment, once subjected to roller compaction, are upgraded in size to larger granules which are less prone to cause ingredient losses during processing or storage.

[0020] Furthermore, since the resulting granulate is of essentially uniform size distribution, the problem of size difference of the initial powdered ingredients is addressed. For example, the ingredient Pyridoxine HCl and Doxylamine Succinate are no longer of different mean particle diameter and are of a mean particle diameter large enough to prevent excessive loss of Pyridoxine HCl during processing.

[0021] Example 1 below is a demonstration of active ingredient loss using a prior art manufacturing method. Example 2 that follows example 1 is a demonstration that such active ingredient loss is negated when practicing the method of the present invention.

[0022] **Example 1 (prior art)**

[0023] Active ingredients, namely Pyridoxine HCl and Doxylamine Succinate were blended with exact quantities of excipients. Five samples of 3 grams were placed into small polyethylene bags and shaken. This mimics the prior art method of placing a final blend of active ingredients and excipients into

polyethylene lined drums prior to emptying said drums into the hopper of a tablet compression machine. After being placed in the small polyethylene bags, the samples were removed and analyzed for content of active ingredients. The results are shown in Table I below:

Table I – Content analysis compared to initial quantity being 100%wt of each of Pyridoxine HCl and Doxylamine Succinate.

Note: values above 100% are attributable to the detection limit of the analysis apparatus.

SAMPLE NO.	PYRIDOXINE HCL IN WT%	DOXYLAMINE SUCCINATE IN WT%
1	76.6	101.3
2	77.6	104.1
3	85.9	101.4
4	85.3	101.4
5	87.1	101.6
Average loss	17.5%	Nil

[0024] This example clearly shows how Pyridoxine HCl is prone to loss during processing and storage. Example 2 below shows how this problem is avoided by the method of the present invention.

[0025] **Example 2**

[0026] The active ingredients, namely Pyridoxine HCl and Doxylamine Succinate were blended with exact quantities of excipients as in Example 1. However, this time the blend was processed using a Chilsonator® Roller compactor to form compacted products that were then crushed and screened to 16 mesh. A series of six 3 grams samples were collected. Two of the samples were directly analyzed for active ingredient content. The four remaining samples were placed in small polyethylene bags and shaken as in Example 1. The samples were then removed from the bags and analyzed for active ingredient content.

[0027] The results are shown in Table II below:

Table II – Content analysis compared to control quantity being about 68.8mg of Pyridoxine HCl per gram of mixture and about 67.5mg of Doxylamine Succinate per gram of mixture.

Note: values above 100% are attributable to the detection limit of the analysis apparatus.

SAMPLE NO.	PYRIDOXINE HCL	DOXYLAMINE SUCCINATE
1 (control)	68.6 mg/g	67.9 mg/g
2 (control)	68.9mg/g	67.1 mg/g
Average of 1 (control) and 2 (control)	68.8mg/g or 100wt%	67.5mg/g or 100wt%
3	95.1 wt% vs. control	99.6 wt% vs. control

SAMPLE NO.	PYRIDOXINE HCL	DOXYLAMINE SUCCINATE
4	95.5 wt% vs. control	100.6 wt% vs. control
5	97.1 wt% vs. control	100.4 wt% vs. control
6	96.5 wt% vs. control	99.4 wt% vs. control
Average loss	3.9 wt% vs. control	Nil

[0028] These results demonstrate that by using the manufacturing method of the present invention, the average loss of Pyridoxine HCl was dramatically lowered when compared to the prior art method.

[0029] It is also to be understood that the method of the present invention can also involve the step of blending the granules resulting from roller compaction to further increase content uniformity of the granular blend. This is done prior to compression into tablet shape or prior to placing the granules in some other suitable dosage form.

[0030] It is also to be understood that the method of the present invention can involve mixing the active ingredients alone, i.e. without excipients, and submitting the active ingredients to roller compaction prior to blending the compacted granules with at least one excipient.

[0031] It is also to be understood that the method of the present invention can involve mixing a single active ingredient (usually the smaller sized active ingredient) with at least one excipient and submitting the mixture to roller compaction prior to blending the compacted granules with at least one other active ingredient and perhaps other excipients.

[0032] It is also to be understood that all mixing steps can be accomplished as sequential mixing of various ingredients with or without intervening sieving or pre-blending steps. The term "mixing" is used in its broad sense of creating a mixture regardless of the exact processing steps used to obtain this mixture.

[0033] When compressed into tablet shape as for an oral or sublingual dosage form, the tablet can be sealed or otherwise coated such as with an enteric coating. The exact coating will of course depend on the intended release site and release rate of the active ingredients once the tablet is ingested.

[0034] Although the present invention has been described hereinabove by way of preferred embodiments thereof, it can be modified, without departing from the spirit and nature of the subject invention as defined in the appended claims.

WHAT IS CLAIMED IS:

1. A method for the preparation of pharmaceutical dosage forms comprising multiple powdered active ingredients, said method comprising the steps of:
   (a) mixing said active ingredients and at least one chosen excipient so as to obtain a powdered mixture;
   (b) compacting said powdered mixture in a roller compactor apparatus to obtain a compacted product;
   (c) breaking and sieving said compacted product to a chosen mesh size to obtain similar sized granules;
   (d) forming said granules into unitary dosage forms.

2. A method for the preparation of pharmaceutical dosage forms comprising multiple powdered active ingredients, said method comprising the steps of:
   (a) mixing said active ingredients and at least one chosen excipient so as to obtain a powdered mixture;
   (b) compacting said powdered mixture in a roller compactor apparatus to obtain a compacted product;
   (c) breaking and sieving said compacted product to a chosen mesh size to obtain similar sized granules;
   (d) mixing said granules with at least one chosen excipient so as to obtain a granular mixture;
   (e) forming said granular mixture into unitary dosage forms.

3. A method for the preparation of pharmaceutical dosage forms comprising multiple powdered active ingredients, said method comprising the steps of:
   (a) mixing said active ingredients so as to obtain a powdered mixture;
   (b) compacting said powdered mixture in a roller compactor apparatus to obtain a compacted product;

(c) breaking and sieving said compacted product to a chosen mesh size to obtain similar sized granules;

(d) mixing said granules with at least one chosen excipient so as to obtain a granular mixture;

(e) forming said granular mixture into unitary dosage forms.

4. A method for the preparation of pharmaceutical dosage forms comprising multiple powdered active ingredients, said method comprising the steps of:

(a) mixing at least one of said active ingredients and at least one excipient so as to obtain a powdered mixture;

(b) compacting said powdered mixture in a roller compactor apparatus to obtain a compacted product;

(c) breaking and sieving said compacted product to a chosen mesh size to obtain similar sized granules;

(d) mixing said granules with at least one other active ingredient so as to obtain a granular mixture;

(e) forming said granular mixture into unitary dosage forms.

5. A method for the preparation of pharmaceutical dosage forms comprising multiple powdered active ingredients, said method comprising the steps of:

(a) mixing at least one of said active ingredients and at least one excipient so as to obtain a powdered mixture;

(b) compacting said powdered mixture in a roller compactor apparatus to obtain a compacted product;

(c) breaking and sieving said compacted product to a chosen mesh size to obtain similar sized granules;

(d) mixing said granules with at least one other active ingredient and at least one other excipient so as to obtain a granular mixture;

(e) forming said granular mixture into unitary dosage forms.

6. The method of any one of claims 1 to 5 wherein the step of forming said granular mixture into unitary dosage forms comprises compressing said granular mixture into a tablet shape.

7. The method of any one of claims 1 to 6 wherein the tablet shape is provided with a coating.

8. The method of any one of claims 1 to 6 wherein said coating is an enteric coating.

9. The method of any one of claims 1 to 5 wherein the step of forming said granular mixture into unitary dosage forms comprises loading said granular mixture into an open capsule and thereafter closing said capsule.

10. The method of any one of claims 1 to 9 wherein the active ingredients comprise Pyridoxine HCl and Doxylamine Succinate.

11. The method of any one of claims 1 to 9 wherein the active ingredients comprise equal parts of Pyridoxine HCl and Doxylamine Succinate.

12. The method of any one of claims 1 to 9 wherein the active ingredients consist of equal parts of Pyridoxine HCl and Doxylamine Succinate.

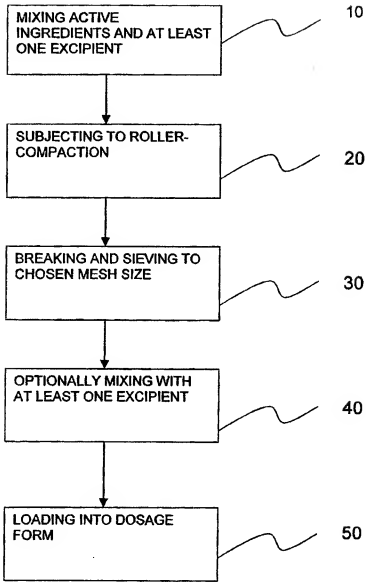
MIXING ACTIVE INGREDIENTS AND AT LEAST ONE EXCIPIENT
10
SUBJECTING TO ROLLER-COMPACTION
20
BREAKING AND SIEVING TO CHOSEN MESH SIZE
30
OPTIONALLY MIXING WITH AT LEAST ONE EXCIPIENT
40
LOADING INTO DOSAGE FORM
50

FIGURE 1